UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF OHIO
WESTERN DIVISION

SHERRI COX, as Administrator of the Estate of Linda S. Beckman, deceased,	**CASE NO: C-1-01-643**
Plaintiff,	**JUDGE BECKWITH** **Magistrate Hogan**
vs.	
METABOLIFE INTERNATIONAL, INC.	
Defendant.	

DEFENDANT METABOLIFE INTERNATIONAL, INC.'S MOTION TO EXCLUDE THE TESTIMONY OF PLAINTIFF'S EXPERTS

NOW COMES Defendant METABOLIFE INTERNATIONAL, INC., and pursuant to Federal Rule of Evidence 702 and 703, moves this Court to exclude the testimony of Plaintiff's experts. The reasons for this motion are more fully explained in the attached Memorandum in Support, which is attached hereto and incorporated by reference herein.

Respectfully submitted,

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MEMORANDUM IN SUPPORT OF DEFENDANT METABOLIFE INTERNATIONAL, INC.'S MOTION TO EXCLUDE THE TESTIMONY OF PLAINTIFF'S EXPERTS

Defendant Metabolife International, Inc., pursuant to Federal Rules of Evidence 702 and 703 and *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993)("*Daubert*"), moves to exclude the opinions of Plaintiff's causation experts that Metabolife 356, a dietary supplement marketed, distributed and sold by Metabolife, taken within the recommended dose, can cause serious or life threatening central nervous system events – hemorrhagic stroke, ischemic stroke, subarachnoid hemorrhage – or serious or life threatening cardiovascular events – heart attack (myocardial infarction) and various cardiac arrhythmias. As shown below, Plaintiff's experts' opinions lack testing, peer review, or indeed, any sound science that justify their admission.

I. Introduction

Metabolife 356 contains the botanical herb ma huang, one of the world's oldest remedies. Ephedrine, the primary active alkaloid of ma huang, has been used in China for more than 5,000 years to treat symptoms of chronic asthma and upper respiratory infections. Rand Report[1] at p. 3, *see, infra,* n. 4. Since the 1930s, ephedrine has been used in the United States to treat asthma. More recently, ephedrine has been used reliably and safely in countless over-the-counter decongestants and cold medicines.

Thus, ephedra, or its alkaloid ephedrine, was a well known - and well tested - substance in 1995 when Metabolife 356 was first introduced to assist in weight loss and to boost energy.

[1] Shekelle P, Morton, S., Maglione M., et al. *Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects*. Evidence Report/Technology Assessment No. 76, AHRQ Publication No. 03-EO22 (Prepared by Southern California Evidence-based Practice Center, RAND, under Contract No. 290-97-0001, Task Order No. 9) ("the Rand Report"). The Rand Report is voluminous and, in an effort not to overwhelm the record, Metabolife attaches here pertinent excerpts thereof. Should the Court desire the entire report, a copy will be provided.

Since that time literally millions of consumers have purchased hundreds of millions of tablets of Metabolife 356. As a result, it is inevitable that some users of the product will have experienced a berry aneurysm - the adverse event which Plaintiff here complains. That does not mean, however, that Metabolife 356 caused these events. To the contrary, the "background rate" of strokes, heart attacks and other serious events - that is, the rate at which the events occur in the population of persons who have not been exposed to the substance - establishes that these events commonly occur throughout the population whether or not the individuals sustaining the adverse events were exposed to Metabolife 356.

The data offered by Plaintiff's experts - "case studies" and other anecdotal "adverse event reports" - fail to control for background rates or other confounding risk factors, and thus this data and any opinions of Plaintiff's experts premised thereon cannot be considered scientifically reliable evidence of causation. Indeed, it was for these reasons that, as recently as one year ago, the Food and Drug Administration ("FDA") concluded that "the types of observed outcomes reported in relationship to the ingestion of ephedrine alkaloids are not uncommon in the general population and therefore the [adverse event] reports alone do not ... establish a link between the reported adverse events and the ingestion of ephedrine alkaloids."[2]

The state of the scientific evidence relating to the safety and efficacy of ephedra/ephedrine was most comprehensively reviewed and summarized in a report authored by the Rand Corporation, an independent and well respected research organization. The Rand Report was commissioned by the United States Department of Health and Human Services, prompted by the recognition that the use of dietary supplements containing ephedra or ephedra-caffeine combinations has generated both publicity and controversy. The concerns can all be

[2] FDA's response to Public Citizen's Petition.

traced to the same source: anecdotal "adverse event reports" or equally uncontrolled "case studies" that purport to find an association between ephedra, or products such as Metabolife 356, and the adverse medical event alleged by Plaintiff here.

The Rand Report, however, reviewed those very case reports and other scientific data and concluded that the present state of the scientific data does not demonstrate that dietary supplements such as ephedra are capable of causing serious medical conditions. Rather, Rand found that further "scientific studies ... are necessary to assess the possible association between consumption of ephedra-containing dietary supplements and ... serious adverse events...," including strokes, heart attacks, and seizures. Rand, p. 221.

Plaintiff's experts have cobbled together data, including general pharmacological properties of ephedrine and caffeine and analogies to other drugs. While apparently recognizing that none of this "evidence," standing alone, sustains their claims, they maintain that this assortment of data, considered in its entirety, is sufficient. Plaintiff's experts' attempts to establish causation with lesser scientific data than that called for by the relevant scientific and regulatory communities are not sufficient to bridge the existing analytic gap, and the law requires exclusion of their generalized and largely speculative theories.

III. Brief Statement of Pertinent Facts

A. Background Concerning Metabolife And Metabolife 356.

Metabolife is a San Diego-based company that markets nutritional herbal and dietary supplements, primarily for weight management. Metabolife 356 is a dietary supplement containing ma huang that has been on the market since about July 1995. Metabolife 356 is a combination of the herb ma huang (ephedrine group alkaloids), guarana (caffeine), and small amounts of other herbs, vitamins and minerals.

Each caplet of Metabolife 356 contains 12 mg. of ephedrine group alkaloids and 40 mg. of caffeine, compared to about 100 milligrams of caffeine in a cup of coffee. The maximum daily serving of Metabolife 356 is 8 caplets, for a daily total of 96 milligrams of ephedrine group alkaloids- within the present FDA guidelines for maximum daily dosage. Two caplets of Metabolife 356 are comparable to the therapeutic doses of ephedrine contained in over-the-counter asthma medications, such as Primatene and Bronkaid. Individual doses of 12.5, 25 or 50 mg. are approved for those drugs, three times a day, *with maximum doses of 120 to 150 mg. per day - higher than the 96 mg. maximum dose recommended by Metabolife* and approved by the FDA.

Since 1996, literally millions of consumers have purchased hundreds of millions of tablets of Metabolife 356.[3] As a result, there is no doubt that some users of Metabolife 356 have experienced an adverse event while taking this product. Because these events occur often in the general population without consumption of Metabolife 356, it is simply a statistical reality that some persons who have taken Metabolife 356 will experience strokes, heart attacks and the other specific events that Plaintiff attempts to attribute to Metabolife. There is simply no proof, however, that the rate of these events is any greater than the background rate or that Metabolife 356 caused these events. Nevertheless, Plaintiff's experts, employing unreliable and unsound data, seek to blame Metabolife for Linda Beckman's ruptured berry aneurysm.

B. Plaintiff's General Causation Experts.

Plaintiff's general causation experts who are the subject of this challenge are the following: (1) Daniel Woo, M.D., neurology; (2) John E. Maggio, Ph.D., pharmacology; (3)

[3] *See,* Rand, p. 3, 6.

Robert J. Gerraughty, Ph.D., manufacturing practices; and (4) Charles R. Buncher, Sc.D., biostatistics and epidemiology.

C. Identification of Defense Experts

In this case, Metabolife's experts are: (1) Guy Rordorf, M.D., neurology, (2) Ramon G. Gonzalez, Ph.D., neuroradiology, (3) Ronald Millard, Ph.D., pharmacology, and (4) Craig A. Molgaard, Ph.D., M.P.H., epidemiology, (5) Gerald Goldhaber, Ph.D., Consumer expectations and Warnings.[4]

II. This Court Is The "Gatekeeper" And Must Exclude Unreliable Expert Testimony

The key issue on this motion is whether the proposed testimony by Plaintiff's experts as to general causation is sufficiently reliable to justify its admission under *Daubert*, 509 U.S. at 589-95. Federal Rule of Evidence 702 imposes a "gatekeeping" responsibility on federal trial courts, requiring judges to "ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable" which should be the "primary locus" of the inquiry. *Daubert*, 509 U.S. at 589; *Vargas v. Lee*, 317 F.3d 498, 500 (5th Cir. 2003)(FRE 702 assigns to the trial judge the task of ensuring that an expert's testimony both rests on a reliable foundation and is relevant to the task at hand).

To fulfill the gatekeeping role, courts must assess both: (1) scientific reliability- "whether the reasoning or methodology underlying the testimony is scientifically valid;" and (ii) relevance or fitness - "whether that reasoning or methodology properly can be applied to the facts in issue." *Daubert*, 509 U.S. at 592-93. The district court's gatekeeping role separates expert opinion evidence based on "good grounds" from subjective speculation that masquerades as scientific knowledge.

[4] By Order of this Court on December 19, 2003, Plaintiff's Motion to Exclude the Testimony of Defendant's Expert Witnesses was denied.

Factors to be considered when the court considers the scientific reliability of an expert's testimony include: (1) whether the expert's theory "can (and has been) tested;" (2) the "known or potential rate of error;" (3) whether the theory "has been subjected to peer review and publication;" and (4) whether the theory enjoys "general acceptance" within the "relevant scientific community." *Daubert*, 509 U.S. at 593-594; see also, *Vargas*, 317 F.3d at 500; *Black v. Food Lion, Inc.*, 171 F.3d 308, 311 (5th Cir. 1999).[5]

The Advisory Committee Notes accompanying Rule 702 also recognize a number of other factors relevant to determining whether expert testimony is sufficiently reliable to be admissible. Such factors include whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion, *General Electric Co. v. Joiner*, 522 U.S. 136, 146 (1997); whether the expert has adequately accounted for obvious alternative explanations, *Claar v. Burlington N.R.R. Co.*, 29 F.3d 499-502 (9th Cir. 1994); and whether the expert "is being as careful as he would be in his regular professional work outside his paid litigation consulting." *Sheehan v. Daily Racing Form, Inc.*, 104 F.3d 940, 942 (7th Cir. 1997); see also *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 152 (1999).

The factors announced in Daubert are not exclusive, and the standard under Rule 702 is flexible. For example, if the expert does not conduct his or her own research, some of the Daubert factors may not "fit." However, even with respect to any such derivative analysis, the district court must still determine whether there is any "objective, verifiable evidence that the testimony is based on `scientifically valid principles.'" *Daubert v. Merrell Dow Pharm., Inc.*, 43

[5] In addition, courts must "be mindful of other applicable rules," including Federal Rules of Evidence 703 and 403. *Daubert, 509* U.S. at *595*. Under Federal Rule of Evidence 703, expert opinions may be based on hearsay only if the "facts or data" relied upon are of a type "reasonably relied upon by experts in the particular field in forming opinions or inferences on the subject." Federal Rule of Evidence 403 allows a court to exclude relevant evidence "if its probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury."

F.3d 1311, at 1316 n. 4, 1317-18 (9th Cir. 1995)("Daubert II"). Thus, "[n]ot every guidepost outlined in Daubert will necessarily apply to expert testimony ... but the district court's `preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid ...' is no less important." *Watkins v. Telsmith, Inc.*, 121 F.3d 984, 990-91 (5th Cir. 1997), citing Daubert, 509 U.S. at 592-93. "Guesswork, even educated hunches by qualified experts, is not enough. **The evidence must be genuinely scientific, as distinct from being unscientific speculation offered by a genuine scientist**." *Molina v. BIC USA, Inc.*, 199 F.Supp. 2d 53, 76 (S.D.N.Y. 2001).

In *Food Lion*, *supra*, for example, the court rejected expert testimony that fibromyalgia could be caused by trauma, based in large measure on a consensus report which reflected general recognition by the scientific community that the existing data - while strongly pointing to trauma as a cause - nevertheless was insufficient to establish causation as a scientific, and therefore, as a legal, matter. The court quoted portions of the report that emphasized the need for further study to definitively establish the causal link:

> Overall ... data from the literature are insufficient to indicate whether causal relationships exist between trauma and [fibromyalgia]. The absence of evidence, however, does not mean that causality does not exist, rather that **appropriate studies have not been performed**.

Food Lion, supra at 312. The court relied on evidence that "experts in the field had determined that the existing evidence was insufficient to establish causal relationships," and because the **further studies called for had not been conducted, Plaintiff's expert's evidence was excluded.** *Id.* at 312.

As Judge Posner has noted, "law lags science, it does not lead it." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996). Courts "must resolve cases... on the basis of scientific

knowledge that is currently available," and only evidence that demonstrates a causal relationship between a product and an alleged injury can be admitted as relevant and reliable. *Moore*, 151 F.3d at 274, 276.

Application of the *Daubert* rule to the facts of this case is straightforward. As the proponent of the expert testimony at issue, Plaintiff has the burden to establish its admissibility "by a preponderance of proof." *Daubert*, 509 U.S. at 593; Fed. R. Evid. 104. Plaintiff must present sufficient expert evidence based on admissible and reliable scientific studies or methodology to be allowed to express their expert opinions on the threshold question of whether Metabolife 356 can cause a berry aneurysm of the same manner and type as Plaintiff's decedent.

The evidence presented in this case is not based on either admissible nor reliable scientific studies or methodologies. Rather, as shown by the Rand Report, recent FDA statements and other studies, the consensus of the relevant scientific and regulatory communities is that causation has not been established, and that further "scientific studies ... are necessary to assess the possible association between consumption of ephedra-containing dietary supplements and ... serious adverse events." Rand, at 221.

Therefore, the current state of scientific knowledge is insufficient to establish a causal link between ephedra, alone or with caffeine, and further study is needed to definitively establish the causal link. As a result, the opinions of Plaintiff's experts in this case are clearly based on lesser evidence, and are therefore, by definition, speculative. They should not be permitted through the evidentiary gate.

Expert testimony is subject to scrutiny precisely because it "can be both powerful and quite misleading" to jurors. *Daubert,* 509 U.S. at 595. As commentators have recognized, courts must rigorously exclude unreliable scientific testimony - otherwise the "ultimate

victims" will be "America's workers and consumers through the increased costs, diminished opportunities, and foregone product availabilities imposed on enterprises engaged in scientific research and development and product manufacturing."[6] The opinions that Plaintiff's experts seek to present to the jury are misleading since they are premised upon wholly unreliable and unscientific evidence. These are exactly the kind of opinions that must be excluded under *Daubert* and its progeny.

III. The Plaintiff's Expert Evidence Is Not Sufficient to Establish General Causation.

As previously set forth in detail in Metabolife's Motion for Summary Judgment, there are no scientific studies which establish Metabolife 356 and ephedra as a cause of a berry aneurysm. In the absence of such studies, Plaintiff's experts have no reliable evidence to support their theory for general or specific causation. The appropriate Daubert protocol in this case requires an assessment of Plaintiff's experts' opinions to measure each of the factors they have identified as supporting a causal connection between Metabolife 356 and Linda Beckman's ruptured aneurysm.

Dr. Daniel Woo

One of Plaintiff's experts, Dr. Daniel Woo, opines that, "Ms. Beckman's use of ephedra led to an increase in blood pressure as evidenced by the increase in blood pressure readings after she began taking ephedra." The basis for this statement is that because ephedra is a sympathomimetic agent, it "usually" increases blood pressure. However, the witness does not state what level increase in blood pressure or heart rate may be expected from taking

[6] Thombrugh, *Junk Science -The Lawyer's Ethical Responsibility,* 25 FordhamUrb. L. J., 449-450(1998)(D*26); see also,* Bernstein, *The Breast Implant Fiasco,* 87 Cal. L. Rev. 457, 459 (1999)(D-5.)(nationwide, the breast implant plaintiffs "never presented any sound scientific evidence that implants cause systemic diseases," yet the lawsuits led to "the bankruptcy of one of the largest corporations in the United States and a nationwide wave of litigation that is yet to subside.").

recommended dosages of Metabolife 356 or whether recommended dosages could cause the formation or rupture of the aneurysm Plaintiff's decedent is describes as having.

Dr. Woo also compares ephedra and ephedrine to other sympathomimetic agents, which as explained below, is not consistent with the standards required by *Daubert*. Moreover, he acknowledges that Linda Beckman smoked ½ a pack of cigarettes per day and that smoking is a recognized role factor for subarachnoid hemorrhage and ruptured aneurysm. Curiously, he ignores any causal effect of smoking the decedent's subarachnoid hemorrhage and aneurysm.

Dr. John Maggio

Another of Plaintiff's experts, Pharmacologist Dr. John Maggio, also discusses general pharmacological properties of ephedrine and other sympathomimetic agents, and reviews anecdotal case reports. He fails to rely however, on a single scientific study that would support the opinion that ephedrine, in the dosage taken by Plaintiff, can cause formation or rupture of a berry aneurysm.

Dr. Robert Gerraughty

Dr. Robert Gerraughty references a review of the practices of Metabolife's manufacturers, but fails to establish any evidence that there was a manufacturing defect in the product the Plaintiff ingested—or that it caused either the formation or rupture of the Plaintiff's berry aneurysm.

Dr. Charles Buncher

Finally, Plaintiff's expert, Dr. Charles Buncher, suggests that use of Metabolife *appears* to increase variability in heart rate, but does comment on what type of variability occurs from taking recommended dosages of Metabolife 356 or whether this variability can cause either the formation or rupture of an aneursym.

Daubert states that whether a theory "can be (and has been) tested" is a key part of the analysis. 509 U.S. at 593. Whether a theory is supported by test results bears directly on two of the indicia of reliability in FRE 702 - whether the testimony is (i) "based on sufficient facts or data;" and (ii) is "the product of reliable principles and methods."

Plaintiff's experts rely on the following :

a. case reports;

b. adverse event reports; and

c. analogies to other sympathomimetics

The fundamental reason why all of the data relied on by Plaintiff's experts do not satisfy Daubert is that it is not supported by methodologically sound testing. The only actual testing - the epidemiological study and placebo controlled clinical trials - found no association between ephedra and any of these conditions.

In addition, Plaintiff's expert testimony does not satisfy other Daubert factors because it is not generally accepted methodology to rely upon such data for a causation opinion and the rate of error cannot be reliably determined. As shown below, such sources of data are not sufficiently based upon generally accepted scientific methods and procedures. Expert opinions based upon such information must be excluded under Daubert and Evidence Rules 702 and 703.

A. Case Reports and Case Series Are Not Scientifically Reliable Proof of Causation.

Although case reports can serve as the basis for a hypothesis that an association exists between an exposure and a disease, they cannot answer (or even test) whether an association actually exists - chiefly because they lack controls. Controls are an essential requirement of any inquiry as to whether a given substance causes a given disease, particularly where, as here, the

given diseases are widespread in the population as a whole, occur frequently, and often occur without exposure to any drug. Without controls, it is impossible to determine whether an association actually exists, or whether observed instances of a disease are actually attributable to the background rate or confounding factors. In a population with a high background rate, attempts to infer causation under these circumstances are valid in only the rarest of instances. Plaintiff's experts do not claim that any such circumstances exist and indeed, they do not.

In a long line of decisions, courts have held that case reports are not sufficiently reliable to support an expert opinion under Daubert. As the Eighth Circuit explained in *Glastetter*, where the plaintiff claimed that a prescription drug caused her stroke: "case reports make little attempt to screen out alternative causes for a patient's condition" and, although they may associate an exposure to one diagnosis of disease, that association is not scientifically valid proof of causation.[7] 252 F.3d at 989-90. Similarly, in *Rider v. Sandoz Pharmaceuticals Corp*., 295 F.3d 1194 (11" Cir. 2002), the Eleventh Circuit affirmed the exclusion of Plaintiff's expert testimony based in large part on case reports. Plaintiffs in *Rider* had suffered hemorrhagic strokes after ingesting Parlodel, a bromocriptine drug. The Eleventh Circuit noted that "[a]lthough a court may rely on anecdotal evidence such as case reports (citation omitted), **courts must consider that case reports ... reflect only reported data, *not scientific methodology***. Some case reports are a very basic form report of symptoms with little or no patient history, description of course of treatment, or reasoning to exclude other possible causes." *Id.* at 1199 (emphasis added).

A number of case reports at issue in *Rider* did contain details of treatment, but the court

[7] Case reports are generated by the clinical process of "differential diagnosis," which is a patient-specific process of elimination that medical practitioners use to attempt to identify the "most likely" cause of a set of symptoms from a list of possible causes. It has been held, however, that differential diagnosis by itself, does not unequivocally prove cause, even for a particular patient. Nor can it be used to establish general causation. Indeed, it assumes that general causation has already been established for the list of possible causes that, under the process, are eliminated one-by-one. Siharath, 131 F. Supp.2d at 1362.

concluded that even the more detailed case reports were not reliable to prove causation "because they report symptoms observed in a single patient in an uncontrolled context." *Id*. According to the court, the detailed reports "may rule out other potential causes of the effect, but they do not rule out the possibility that the effect manifested in the reported patient's case is simply idiosyncratic or the result of unknown confounding factors." *Id*.

Similarly, in *Miller v. Pfizer, Inc*., 196 F.Supp. 2d 1062, (D. Kan. 2002), independent experts were appointed by the Court to determine whether plaintiff's expert had followed generally accepted scientific methodology in reaching his opinion that Zoloft caused Plaintiff's 13 year old son to commit suicide. The independent experts noted that:

> determining the strength of an association requires at least two groups of subjects, one exposed to the agent of interest (sertraline), the other not so exposed, so that rates of the outcome event (suicide) can be determined and compared .... [T]he lack of a comparison group ... would make a series of case reports unsuitable for determining the quantitative strength of an association, regardless of other attributes.

Id. at 1076. See also, Siharath, 131 F. Supp.2d at 1361-1363, and the cases cited therein.

B. Adverse Drug Reaction Data Are Not Scientifically Reliable Proof of Causation.

At the lowest level of evidentiary and epidemiological hierarchy are "call in" reports made to various entities. There are three kinds of such "call in" records here - reports called in to the FDA, reports called in to Metabolife, and reports called in to various Poison Control Centers throughout the country. This type of data brings meaning to the word "anecdotal." Under Daubert, adverse event reports do not support expert testimony on causation. "[A]dverse drug experience reports ... [are] not controlled studies and do not eliminate confounding variables," and thus "are insufficient to establish the requisite causation." *Hollander*, 95 F.Supp.2d at 1237; accord *Brumbaugh v. Sandoz Pharm. Corp.*, 77 F. Supp.2d, 1153, 1157 (D. Mont. 1999)

(adverse event reports "are compilations of occurrences, and have been rejected as reliable scientific evidence supporting expert opinion so as to meet the requirements set forth in Daubert").

The FDA itself does not consider adverse event reports as proof of causation.[8] And the Rand Corporation similarly concluded that "the majority of FDA case reports are insufficiently documented to make an informed judgment about the relationship between the use of ephedra containing supplements and the adverse event in question." Rand Report, p. 221. Records called in to Metabolife have also been rejected as establishing any sort of basis for determining causation. This position was affirmed recently by the United States General Accounting Office ("GAO"). At the request of the Chairman of the House Subcommittee on Human Rights, the GAO reviewed over 14,000 call records provided by Metabolife. D-12 .48 The GAO concluded: "We cannot establish that any of the adverse events reported in the Metabolife International call records were caused by Metabolife 356." Id., p. 14. Even the most recent publications by the FDA and GAO rely on adverse event reporting and could ""sentinel events," because they may indicate a safety problem but do not prove that ephedra caused the adverse event. The study recognized that such case studies are a limited form of scientific evidence. On July 24, 2003, the commissioner of the FDA stated that "sentinel events indicative of a potential safety problem [are] not enough alone to make an empirical, scientific determination with a high degree of statistical confidence that ephedra causes serious adverse events." (July 24, 2003 Statement of Mark B. McClella, M.D., Ph.D., Commisioner of the Food an Drug Administration before the Subcommittee on Commerce, Trade and Consumer Protection and the Subcommittee on

[8] 21 C.F.R. §600.80(1) states: "a report or information submitted by a licensed manufacturer under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the licensed manufacturer or FDA that the report or information constitutes an admission that the biological product caused or contributed to an adverse effect."

Oversight and Investigations Committee on Energy and Commerce United States House of Representatives, attached.)

C. Analogy to Other Drugs Is Not Scientifically Reliable Proof That Ephedra In the Doses Recommended by Metabolife 356 Causes Aneurysms.

To the extent that Plaintiff's experts rely on studies involving drugs other than ephedra/ephedrine to extrapolate the effects of products containing ephedra in the body, their proposed opinions are not scientifically reliable. Ephedra and ephedrine are sympathomimetic substances, meaning that they mimic certain aspects of the sympathetic nervous system. Sympathomimetics are a broad group of drugs that act, to varying extents, throughout body and encompass a wide variety of compounds (e.g., other decongestants such as pseudoephedrine, drugs used in cold remedies such as phenylpropanolamine ("PPA") and drugs of abuse such as amphetamines), each of which is unique in structure and action. All sympathomimetics cannot be considered as one. Some agents, like norepinephrine, cause vasoconstriction in various blood vessels. Others, like dobutamine and isoproterenol, cause vasodilation.

It is untrue and inaccurate to suggest that all sympathomimetic drugs raise blood pressure, and it does not automatically follow that just because one member of a class exerts a particular effect, all of the others will also. Plaintiff's experts nevertheless inappropriately lump together ephedrine with other sympathomimetic drugs in an attempt to support their opinion that ephedrine is capable of causing hemorrhagic stroke and other injuries alleged. They do so in spite of the fact that the pharmacologic effects of ephedrine are different than those of the other drugs from which they extrapolate, including PPA, amphetamine, cocaine, and pseudoephedrine. They also do so in spite of the finding of Morgenstern, et al., in which the authors re-evaluated the case control study group they used to establish a statistically significant causal relationship between PPA use and hemorrhagic stroke and found no such relationship between the use of

ephedra and hemorrhagic stroke. The findings of Morgenstern, et al. suggest that ephedra and PPA do not have the same effects on the human body. The dangers of basing causation on such generalities is well established. As numerous courts have recognized, even "slight differences in molecular structure can cause seemingly similar compounds to have radically different biological effects." *Soldo v. Sandoz Pharm. Corps.*, 244 F.Supp.2d 434, 445 (W.D. PA. 2003); *Weisgram v. Marley Co.*, 528 U.S. 440 (2000),("[S]mall differences in molecular structure often have significant consequences."); accord *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1207 (10th Cir. 2002)("[S]mall differences in chemical structure may produce substantial differences in physiological effects.").

III. The General Consensus Of The Relevant Scientific And Regulatory Communities Is That The Present State Of The Scientific Evidence Is Not Sufficient To Establish Causation And That Further Testing Is Necessary To Establish Any Such Causal Link.

As discussed throughout this Memorandum, the state of the scientific evidence relating to ephedra was recently summarized in the Rand Report commissioned by the United States Department of Health and Human Services. Rand investigators were asked to look at three different areas - safety and efficacy of ephedra as a weight loss agent, safety and efficacy of ephedra as used to enhance athletic performance and adverse events associated with dietary supplements containing ephedra. With respect to the investigation into adverse events associated with dietary supplements containing ephedra, Rand was asked to review the available scientific literature for answers to many of the same questions now before the Court in this case. In responding to this charge, the researchers conducted an exhaustive search for all literature relating to ephedra- the botanical extraction - or ephedrine, the synthetic version. The Rand Report identified and considered 50 placebo controlled clinical trials of ephedra/ephedrine, listed

at pages of the report; see also, pp. 86,24. Many of these are the same trials discussed and relied on by the defense experts in this case.

The Rand Report recognized "[n]o serious adverse events (e.g., death, myocardial infarction, stroke, etc.) were reported in the 52 clinical trials that reported sample sizes. Therefore, the rate for these adverse events is zero." *Id*. at 88; emphasis supplied. Rand determined, however, that the studies were too small to detect rare (1 in 1,000 type events), but serious adverse events. *Id*. at 221. Accordingly, the researchers resorted to a review of case reports, but concluded that "***a causal relationship between ephedra or ephedrine use and these events cannot be assumed or proven***" by case reports. *Id*., p. xvi; emphasis supplied.

It should be noted that Rand did find a possible association between ephedra/ephedrine and some minor adverse events," such as nausea, vomiting, anxiety and palpitations, *Id*. at 220-221. That is, quite frankly, not totally surprising as almost all substances can, under some circumstances of use, be found to be connected with some minor reactions. But as to "serious adverse events," Rand could not establish any causal link within the generally accepted scientific criteria for determining causation. The "serious adverse events" as to which a causal link was rejected included ventricular tachycardia/fibrillation (rapid heart beat); cardiac arrest, pulmonary arrest, transient ischemic attack (TIA), and brain hemorrhage. See Rand Report, p.27.

The Rand Report concluded that establishing causation for any of the serious adverse events described above is impossible based on the current scientific data. In recognition of this scientific reality, the Rand Report pleads for scientific studies, not additional case reports, to establish – or negate - a causal link:

> Scientific studies (not additional case reports) are necessary to assess the possible association between consumption of ephedra-containing dietary supplements and these serious adverse events. Given the rarity of such events, a properly designed case control

> study would be the appropriate next step. Such a study would need to control for caffeine consumption.

Id. at 221 (emphasis added). The researchers advised: "Continued analysis of case reports cannot substitute for a properly designed study to assess causality." *Id.* at 223.

The Rand Report represents the state of the scientific knowledge to date with respect to ephedra and the very same medical events that Plaintiff attempts to attribute to Metabolife 356. This report establishes that the hypothesized causal link between Metabolife 356 and the events that Plaintiff attempts to attribute to it has not remotely been established. Thus, it is the consensus of the relevant scientific community that the present state of scientific knowledge is not sufficient to prove or disprove the hypothesis that ephedra/ephedrine, alone or with caffeine, is capable of causing any of the serious adverse events asserted by Plaintiff here.

The relevant regulatory community, the FDA, has also determined that the present state of the science is insufficient to establish a causal link between ephedra use and serious adverse cardiovascular events. About a year ago, on June 14, 2002, the FDA responded to a petition filed by the Public Citizen's Health Research Group ("Public Citizen's") which sought to ban the sale and production of dietary supplements containing ephedra alkaloids such as Metabolife 356.[9]

In its response, the FDA advised Public Citizen's that "the adverse event reports regarding ephedrine alkaloids cited in [the Public Citizen's] petition do not provide a scientific basis for assessing the safety of ephedrine alkaloids" and that further study is needed. D-9. Department of Health and Human Services Secretary Thompson explained the FDA's position as follows: [The] FDA has received reports of adverse events regarding the ingestion of dietary

[9] FDA's response to Public Citizen's petition ("FDA's Response").

supplements containing ephedrine alkaloids. Some of these reports have included serious cardiovascular and central nervous system events.

The primary purpose of a voluntary adverse event reporting system is to generate "signals" of potentially related events, rather than assessing product safety. Additional research is generally required to further define the relationship between the ingestion of a particular product and the types of adverse event reports received. There are situations where background rates of the observed event are so rare or unusual that, in combination with physiologic responses and biologic plausibility, a significant relationship between the events is self-evident from the reports in a voluntary reporting system. However, the FDA has advised that the types of observed outcomes reported in relationship to the ingestion of ephedrine alkaloids are not uncommon in the general population and therefore the reports alone do not provide a scientific basis for assessing the safety of ephedrine alkaloids or establish a link between the reported adverse events and the ingestion of ephedrine alkaloids. Even the most recent whitepaper releases by the FDA indicate that current studies “do not establish deifintive causal evidence of a statistically significant elevated risk of death or serious injury from ephedra.” (FDA “Whitepaper on Ephedra, released February 28, 2003). FDA has determined that questions remain on the likelihood and strength of association between ephedrine alkaloids and the adverse events reported to the FDA.

IV. Conclusion

The current state of the scientific evidence is simply not sufficient to establish that Metabolife 356 alone or with caffeine can cause an aneurysm. Other courts have rejected attempts to lower Rule 702's evidentiary bar in order to conform to the available evidence. Though Plaintiff’s experts may sincerely believe that they have done the best analysis possible

with the available data, those beliefs do not enhance the reliability of their testimony. See *Total Containment, Inc. v. Dayco Prods., Inc.*, 2001 WL 1167506 at *7 (E.D. Pa. 2001)(if enough relevant data to support methodology are simply unavailable, methodology will have infinite error rate); *In re: Diet Drugs*, 2001 WL 454586 at * 13(excluding expert testimony of scientist who failed to conduct blinded test, even fact that it was conduct of adverse party which prevented blinding does not make testimony any more reliable); *Pappas v. Sony Electronics, Inc.*, 136 F. Supp.2d 413, 426 (W.D. Pa. 2000) (excluding testimony of expert pursuant to Daubert, although expert carefully examined available evidence and although fire destroyed large portion of evidence needed to prove fire's cause).

WHEREFORE, consistent with those principles, and for all of the reasons set forth above, Metabolife respectfully urges this Honorable Court to grant its Motion, and to exclude Plaintiff's experts' opinions and testimony on causation.

Respectfully submitted,

Sutter, O'Connell, Mannion & Farchione Co. L.P.A.

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CERTIFICATE OF SERVICE

I certify that a true copy of the foregoing *Defendant Metabolife International, Inc.'s Motion to Exclude the Testimony of Plaintiff's Experts* was forwarded to the following via U.S. regular mail on this 23rd day of December, 2003 to:

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